Tetrahedron Letters, Vol.22, No.40, pp 4017 - 4020, 1981
Printed in Great Britain

0040-4039/81/404017-04$02.00/0

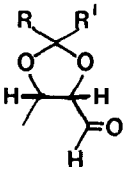
SYNTHESIS OF N-BENZOYL-L-DAUNOSAMINE FROM D-THREONINE

Claudio Fuganti, Piero Grasselli and Giuseppe Pedrocchi-Fantoni

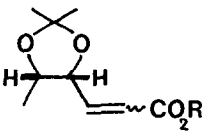
Istituto di Chimica del Politecnico, Centro del CNR per la Chimica delle Sostanze Organiche Naturali, 20133 Milano, Italy

The synthesis of N-benzoyl-L-daunosamine (14) from the C_4 threo aldehyde (2b), prepared from D-threonine, through the intermediacy of the C_7 adduct (7a) is reported

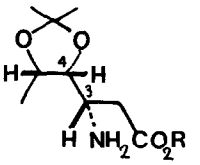
We have recently reported on chiral preparations of N-acyl derivatives of the amino deoxy sugar L-daunosamine[1] and of its configurational isomers[2,3] starting from the C_4 erythro and threo aldehydes (1a) and (2a). Compound (1a) was prepared from a product obtained from cinnamaldehyde and bakers'yeast, whereas (2a) was obtained from natural tartaric acid or from D-threonine. The synthetic procedures involve the construction from (1a) and (2a) of the C_6 α,β - unsaturated esters (3) and (4), respectively. These compounds, in turn, add ammonia stereoselectively to give the β-amino esters (5) and (6), with threo stereochemistry relative to positions 3 and 4. The latter intermediates gave rise, via the corresponding lactones, to the L-arabino and L-xylo amino deoxy sugar derivatives (13) and (11). The required L-lyxo isomer (14) has been obtained from compounds of the L-arabino series by inverting the configuration at C-4. Similarly,. the L-ribo isomer (12) was prepared from the corresponding intermediate in the L-xylo series.



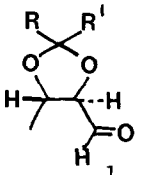
(1a) R= R^1= Me
(1b) R-R^1= $(CH_2)_4$



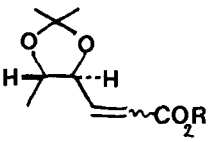
(3)



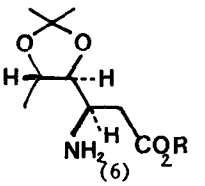
(5)



(2a) R= R^1= Me
(2b) R-R^1= $(CH_2)_4$



(4)

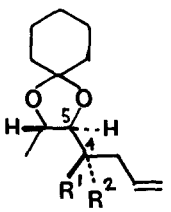


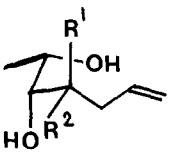
(6)

While the above procedure seems satisfactory for the preparation from (1a) and (2a) of N-trifluoroacetyl-L-acosamine and of the L-xylo isomer (11), it appears as less efficient for the synthesis of the most important component of the series, namely,

N-trifluoroacetyl-L-daunosamine, the major operational drawback being represented by the inversion of configuration at C-4 required in the conversion L-arabino→ L-lyxo. Accordingly, we have been interested in a synthesis of N-acyl-L-daunosamine from the threo C_4 aldehyde (2) allowing the intact incorporation into the amino deoxy sugar of the chirality present in (2).

We now present the results of our studies in this area. Thus, the aldehyde (2b)•, upon treatment with an excess of $BrMgCH_2CH=CH_2$ in tetrahydrofuran, at -78°C, gave in ca. 75% yield the C_7 adduct (7), shown by g.l.c. analysis[4] to be a 8:2 mixture of two products, which we were unable to separate by conventional SiO_2 column chromatography . The mixture showed $[\alpha]_{20}^{D}$ -14° (c 1, EtOH). This material was treated for 2 d at 0°C with a large excess of 4-toluenesulphonyl chloride in pyridine to give in 85% yield the tosylate (8). Azide displacement (NaN_3, NH_4Cl in dimethylformamide, 100°C, 24 h) gave the azide (9) (80% yield), showing a single spot on t.l.c., $[\alpha]_{20}^{D}$ -20° (c 1, EtOH). However, g.l.c. analysis[5] indicated it to be a 2:8 mixture of two components.





(7a) R^1= OH; R^2= H
(7b) R^1= H; R^2= OH

(8a) R^1= OTs; R^2= H
(8b) R^1= H; R^2= OTs

(9a) R^1= H; R^2= N_3
(9b) R^1= N_3; R^2= H

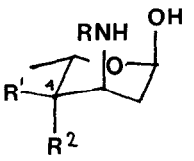
(10a) R^1= H; R^2= $NHCOC_6H_5$
(10b) R^1= $NHCOC_6H_5$; R^2= H

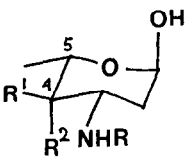
Reduction of (9) ($LiAlH_4$ in Et_2O) gave an amine which, upon sequential treatment with 50% aqueous acetic acid (2 h at 100°C) and benzoyl chloride in alkaline conditions (K_2CO_3, aqueous acetone), gave rise, after extraction with CH_2Cl_2, in ca. 65% yield to the N-benzoyl derivative (10), showing two separate spots on t.l.c.. The crude mixture separated from boiling ethyl acetate- hexane a crystalline material, m.p. 135-137°C, $[\alpha]_{20}^{D}$ 21.6 (c 1, EtOH), in ca. 55% yield. The latter compound upon ozonolysis in MeOH at -20°C, followed by Me_2S treatment, yielded 85% N-benzoyl-L-daunosamine

---

• (2b) was prepared from D-threonine upon treatment with: (i) $NaNO_2$, H_2SO_4; (ii) MeOH, H_3O^+; (iii) cyclohexanone, TsOH, benzene; (iv) $NaAlH_2(OCH_2CH_2OMe)_2$, Et_2O, -50°C, 4 h. (2b) was obtained in step (iv) in 50% yield (85% based on recovered ester), purified on column chromatography (SiO_2) with hexane. 90% pure by glc.

(14), identified as optically pure by comparison with an authentic sample,[6†] partly obtained as crystalline precipitate from the crude evaporated reaction mixture (from ethyl acetate-methanol), and the remaining through chromatoghraphy on a short SiO_2 column with ethyl acetate. The mother liquors from which the benzoyl derivative giving rise to (14) had been separated were taken to dryness and ozonised, as above, to give, eventually, after chromatography, N-benzoyl-L-xylo-2,3,6-trideoxy-3-amino-hexose (11) and (14), in ca. 1:2 ratio.





(11) R= COC_6H_5; R^1= H; R^2= OH
(12) R= COC_6H_5; R^1= OH; R^2= H
(13) R= COC_6H_5; R^1= OH; R^2= H
(14) R= COC_6H_5; R^1= H; R^2= OH

The above results allow to assign structural formulas (10a) and (10b), with erythro and threo configurations relative to positions 4 and 5 to the compounds giving (14) and (11), with lyxo and xylo configurations, respectively. Furthermore, in view of the inversion of configuration at C-4 expected to occur in the tosylate → azide conversion, it follows that the addition of $BrMgCH_2CH=CH_2$ on the α,β -dialkoxy aldehyde (2b) occurs with ca. 8:2, threo: erythro stereocontrol in agreement with previous observations in this area.[7] Also, the threo: erythro ratio (7a): (7b) is not significantly affected carrying on the reaction at -120°C.

Exploratory experiments with the aldehyde (1b) have shown that the addition of $BrMgCH_2CH=CH_2$ occurs with a lower degree of stereocontrol. Indeed, from (1b) two separable C_7 adducts have been obtained in ca 4:6 ratio, the major isomer being the erythro one, as shown by its conversion through the abovementioned reaction sequence into N-benzoyl-L-acosamine (13). However, since the two isomeric materials can be interconverted by inverting the configuration at C-4 ($(C_6H_5)_3P$, benzoic acid, diethylazodicarboxylate, followed by NaOH hydrolysis) , also this reaction might be synthetically useful. Work in this field is in progress.

We thank Farmitalia-Carlo Erba, SpA, Milano, for a grant (to G.P.F.).

† kindly provided by drs. G.Cassinelli and S.Penco of Farmitalia-Carlo Erba

REFERENCES

[1]G.Fronza, C.Fuganti and P.Grasselli, J.Chem.Soc.Chem.Commun.,1980,442

[2]G.Fronza, C.Fuganti, P.Grasselli and G.Marinoni, Tetrahedron Letters,1979,3883

[3]G.Fronza, C.Fuganti and P.Grasselli, Tetrahedron Letters,1980,2999

[4]180X 0.2 (int. diam) Pyrex column with 5% SP 1000 on Supelcoport 100/120 mesh; 170 → 220°C, 5°×min.; 8' isoth.

[5]analysis conditions as above; the peak intensities are reversed

[6]F.Arcamone, G.Cassinelli, G.Franceschi, R.Mondelli, P.Orezzi, and S.Penco, Gazzetta, 1970,100,949

[7]W.Clark Still and J.A.Schneider, Tetrahedron Letters,1980,1035

This work has been financially supported by: Piano finalizzato CNR Chimica fine e secondaria

(Received in UK 17 July 1981)